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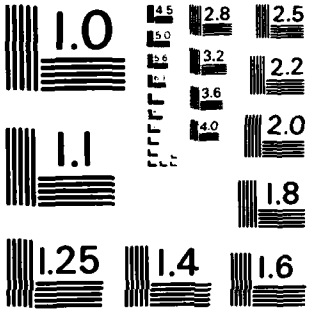

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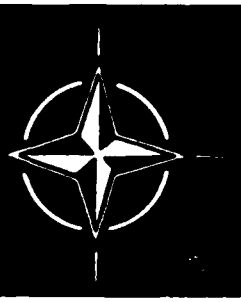

THE ONCOGENIC HAZARD FROM CHRONIC INHALATION OF HYDRAZINE

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SUMMARY

Hydrazine is used in the United States Department of Defense as a bipropellant mixture with unsymmetrical dimethylhydrazine in missile operations, as a monopropellant to power aircraft emergency power systems, and as an oxygen scavenger in shipboard boiler water treatment. It also finds a wide variety of uses in the civilian community. For more than a decade it has been known that hydrazine administered orally at high doses in mice caused increased tumor formation. However, no data were available to evaluate the cancer-producing hazard from occupational inhalation exposures. Studies were therefore conducted to evaluate the long-term effects of airborne hydrazine at levels near the present and proposed Threshold Limit Value concentrations. Repeated daily inhalation exposure to 5 parts per million (ppm) hydrazine induced nasal tumors in Fischer 344 male and female rats and in male Golden Syrian hamsters. Repeated exposure to 1 ppm also produced nasal turbinate tumors in rats and pulmonary adenomas in female C57B1/6 mice. The inhalation exposures to the rodents were conducted for 6 hours per day, 5 days per week over a 12-month period. The hamsters were held for an additional 12-month postexposure observation period and the survivors were necropsied. Rats and mice were held 18 months postexposure. The nasal turbinate tumor incidence in rats was dose related. Increased tumor incidence occurred in both mice and hamsters at the maximum tolerated repeated inhalation dose. No statistically significant tumorigenic effects occurred after repeated exposure to 0.05 and 0.25 ppm hydrazine concentrations which spanned the American Conference of Governmental Industrial Hygienists recommended Threshold Limit Value.

BACKGROUND

Hydrazine (N_2H_4) is a highly reactive reducing agent which is widely used as an intermediate in organic synthesis and either singly or in combination with other hydrazines as a missile propellant. An important and increasing use of hydrazine is that of a boiler feed water additive as an oxygen scavenger. It is a colorless polar liquid, weakly basic, and it fumes in air. It has a slightly ammoniacal odor.

Clark[1] provided a detailed review of the toxicology and pharmacology of propellant hydrazines. Hydrazine is a strong convulsant at high doses but may cause central nervous system depression at lower doses. Animals may die acutely of convulsions, respiratory arrest, or cardiovascular collapse within a few hours of an acute exposure by any route of administration, or may die two to four days later of liver and kidney toxicity.[2,3] Jacobson et al.[4] reported the 4-hour LC_{50} value as 252 ppm (330 mg/m^3) for the mouse and 570 ppm (750 mg/m^3) for the rat. House[5] exposed monkeys, rats, and mice to a hydrazine concentration of 1.0 ppm continuously for 90 days. Though mortality was very high, some animals survived. Ninety-six percent of the rats and 98% of the mice died during the exposure, while monkeys proved to be the most resistant species with only a 20% mortality. Comstock et al.[6] exposed dogs, in separate experiments, to 5 and 14 ppm. Two dogs survived the repeated six-hour exposures to 5 ppm hydrazine for six months, and two of four dogs lived after 194 six-hour exposures to 14 ppm. Two of four dogs died during the third and fifteenth weeks in a debilitated condition. The dog that died during the fifteenth week had a severe convulsive seizure prior to death. Prior to death, both dogs showed signs of anorexia and general fatigue. Changing diets and forced feedings resulted in the survival of the remaining two dogs.

A six-month chronic inhalation study of hydrazine was reported by Haun and Kinkead[7] which employed four exposure groups and an unexposed control group. Each group was comprised of 8 male beagle dogs, 4 female rhesus monkeys, 50 male Sprague-Dawley rats, and 40 female ICR mice. The experimental groups were exposed to vapors of hydrazine either at concentrations of 1.0 or 0.2 ppm continuously, or at 5.0 and 1.0 ppm intermittently. The continuous exposures were designed to approximate the same weekly doses of hydrazine received by the intermittent exposure groups, with continuously exposed animals receiving 168 and 33.6 ppm-hours of hydrazine/week and intermittently exposed animals 150 and 30 ppm-hours/week. Dogs exposed at the higher dose levels, either intermittently or continuously, exhibited 10-20% reductions in erythrocyte, hematocrit, and hemoglobin values which continued throughout the six-month exposure but returned to

control values within two weeks after the exposure ended. Hematology values for dogs exposed to lower doses remained within the normal limits of the control group.

Rats showed a dose-related growth rate depression and a sustained difference in group average weights of up to 35 grams throughout the exposure. Weight loss in dogs which occurred only in the high dose group was recovered within two weeks postexposure, suggesting that the loss was due to appetite suppression. Gross and microscopic examination of tissues from these animals taken at termination of the exposure showed fatty liver changes in mice and dogs at the high exposure dose levels but no exposure-related changes in the livers of monkeys and rats.

Ten mice and 10 rats from each of the exposure groups were held for a year postexposure period. Most of the rats in the two high dose groups died within 6-8 weeks postexposure from chronic pulmonary disease. This infection spread to the other groups housed in the same animal room. Consequently, none of the rats survived long enough to evaluate the carcinogenic potential of inhaled hydrazine for this species.

Approximately half of the mice in each group were alive one year postexposure. Tumorigenic changes in these mice were reported by MacEwen et al. in 1974.[8] Mice exposed to the high doses (continuous exposure to 1 ppm hydrazine or intermittent exposure to 5.0 ppm) had increased incidences of alveolargenic carcinomas, lymphosarcomas, and hepatomas. Both lower dose groups had an increased incidence of alveolargenic carcinomas when compared with unexposed controls. The total tumor incidence appeared to be dose related: approximately 87% tumor incidence occurred at the high dose level; 33% at the low dose level; and 12% in the unexposed control group. Although the group sizes were very small, the findings were important in that they demonstrated tumorigenic response at the current Threshold Limit Value.

Since hydrazine inhalation at the Threshold Limit Value increased the incidence of pulmonary tumors in mice, a more comprehensive oncogenic study of hydrazine effects on multiple species was undertaken.

EXPERIMENTAL DESIGN AND RESULTS

The objectives of this study were to evaluate (a) the chronic effects of inhaled hydrazine on rats, mice, hamsters, and dogs and (b) the oncogenic potential of hydrazine in rodents observed for a maximum period of 1-1/2 years after one year of industrial-type inhalation exposure. The animals used in this study were C57B1/6 mice obtained from the Jackson Laboratories, CDF (Fischer 344 derived) albino rats from Charles River, Engle Golden Syrian hamsters, and beagle dogs. The number of animals of each species and sex are listed in Table 1 which also shows the exposure concentrations.

TABLE 1. EXPERIMENTAL DESIGN FOR HYDRAZINE INHALATION EXPOSURE CONCENTRATIONS

Hydrazine Concentration, ppm	Species and Sex	Number of Animals
0.05	Rats, male	100
	Rats, female	100
	Mice, female	400
0.25	Hamsters, male	200
	Mice, female	400
	Rats, male	100
	Rats, female	100
	Dogs, male	4
	Dogs, female	4
1.0	Hamsters, male	200
	Mice, female	400
	Rats, male	100
	Rats, female	100
	Dogs, male	4
	Dogs, female	4
5.0	Rats, male	100
	Rats, female	100
	Hamsters, male	200
Control	Rats, male	150
	Rats, female	150
	Mice, female	800
	Hamsters, male	200
	Dogs, male	4
	Dogs, female	4

The exposure concentrations were selected to span the range from a certainly toxic level to the current Occupational Safety and Health Administration (OSHA) Threshold Limit Value for exposure to hydrazine (1 ppm) and the proposed American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value of 0.1 ppm. The 5 ppm exposure concentration was selected as a maximum tolerable exposure dose which would

produce some biological response without causing death in hamsters and rats. Mice and dogs were not exposed at this concentration, because prior studies (Haun and Kinkead[7]) had shown that repeated daily exposures to 5 ppm hydrazine caused death in these species.

The inhalation exposures were conducted on a 6 hour/day, 5 day/week schedule for a one-year period without exposures on weekends and holidays. The animals were exposed in Thomas Dome exposure chambers (Thomas[9]) at a slightly negative pressure (725 mm Hg) to insure a complete seal and to prevent contamination of the surrounding laboratories and personnel. All animals were observed hourly during the 12-month hydrazine exposure phase of the study and daily during the postexposure phase. Rats, dogs, and hamsters were weighed individually at biweekly intervals during exposure and monthly during the postexposure period. Mice were weighed in cage groups and group means followed on a monthly schedule throughout the entire study.

Blood samples were drawn from dogs at biweekly intervals during the exposure phase and clinical determinations made for the following battery of tests:

RBC	Glucose
WBC	Total Protein
HCT	Albumin
HGB	Globulin
Sodium	A/G Ratio
Potassium	SGPT
Calcium	Alkaline Phosphatase

Animals that died or were killed during the study were necropsied following the National Cancer Institute protocol. The necropsy consisted of an external examination, including all body orifices, and the examination and fixation of portions of approximately 44 tissues.

Although not dose dependent, growth was reduced in all hydrazine-exposed rats during exposure, but the effect was most significant in the male rats exposed to the 5 ppm concentration. The differences between exposed and control animals were maintained at relatively constant levels during the first 12 months postexposure but became less significant during months 25 to 30 of the study as the weight decline of the aging animals was observed. The effect of depressed growth in female rats was not as pronounced as in males during the exposure phase but was significant and became more noticeable during the postexposure observation period. Hamster body weights were depressed for all exposure groups but also exhibited an inexplicable cyclic phenomenon common to all groups exposed as well as the unexposed that was relatively severe in all groups. In the final months, only the 5 ppm hydrazine exposed group continued to show a significant weight difference from controls. Mice were not exposed to the 5 ppm hydrazine atmosphere. Body weights of mice were unaffected by chronic exposure to inhaled hydrazine at 1 ppm or less.

There was no significant increase in the mortality experience of the hydrazine-exposed mice, rats, hamsters, or dogs. Gross histopathologic examinations were performed on all rodents that died during the course of the study or were sacrificed at completion of the postexposure period. Histopathologic examinations were conducted in accordance with the National Cancer Institute protocols on approximately 33 tissues from all animals with the exception of a few in which postmortem changes were extensive or cannibalism prevented examinations.

Surviving hamsters were sacrificed one-year postexposure, and their tissues were examined by pathologists of the Veterinary Science Division at Brooks Air Force Base, Texas. Tumor and nontumor nomenclature was developed by this group for automated data processing of the results from hamsters. Tumor incidence tables were compiled, and statistical analyses, using the Fisher Exact Test, were performed by the University of California, Irvine, staff. Since rat mortality was very low after one-year postexposure, 10% of the survivors were sacrificed and tissues collected as previously described. The study was terminated after 30 months (18 months postexposure), and all surviving rats were necropsied. Mouse mortality approached 90% in the 18th postexposure month for the first set of animals including the 0.05 ppm and 0.25 ppm hydrazine-exposed mice and their controls. The second set of mice, including the 1 ppm hydrazine exposure group and their controls, was terminated at 132 weeks which was 3 weeks longer than the first set. Tissues from both rats and mice were sent to the Huntingdon Research Centre in Huntingdon, England, for histopathologic examination. Rats were examined by Dr. C.P. Cherry and mice by Dr. J.M. Offer under the supervision of Dr. D.E. Prentice.

Table 2 shows the tumor incidence in the various groups of exposed and control hamsters. The outstanding finding in hamsters is a statistically significant increase in benign nasal polyps. These tumors were seen in 16/160 of the 5 ppm exposed animals; only one in the control group. The only other tumor types of possible importance are those of the colon in the 5 ppm exposure group. There were three primary adenocarcinomas, one benign leiomyoma, and one benign papilloma. When these tumor types were separately subjected to the Fisher Exact Test, none showed statistical significance. There was a rather large incidence of cortical adenomas in the adrenals of all groups of exposed hamsters but with incidence rates lower than that in the control group. This type of tumor is commonly seen in aged hamsters. Incidence of other tumors in the various organs was low. No biological significance is attached to the increase in benign thyroid

adenomas limited to the 0.25 ppm hydrazine exposure group. The reduced incidence of adrenal cortical adenomas may indicate some antineoplastic activity as will also be seen with leukemia incidence in rats.

TABLE 2. TUMOR INCIDENCE IN CONTROL AND HYDRAZINE-EXPOSED MALE GOLDEN SYRIAN HAMSTERS†

TUMOR TYPE	Unexposed Controls	0.25 ppm Exposed	1.0 ppm Exposed	5.0 ppm Exposed
Nares, Trachea, Bronchi				
Polyp (B)	1/181	0/154	1/148	16/160**
Basal Cell (P)	0/181	0/154	1/148	0/160
Basal Cell (B)	0/181	0/154	0/148	1/160
Adenoma (P)	0/181	1/154	0/148	0/160
Adenoma (B)	0/181	0/154	0/148	2/160
Lung				
Bronchogenic Adenoma (P)	1/179	0/154	1/146	0/155
Bronchogenic Adenoma (B)	0/179	0/154	0/146	2/155
Liver				
Reticulo-endotheliomas (B)	1/180	0/160	0/148	0/159
Spleen				
Hemangioma (P)	1/160	1/129	0/130	2/138
Reticulo-endotheliomas (P)	1/160	2/129	0/129	0/138
Reticulo-endotheliomas (B)	1/160	0/129	0/129	0/138
Bone Marrow, Blood				
Myelogenous (P)	0/157	0/134	1/136	0/135
Bone				
Osteoma (P)	0/177	0/152	0/148	1/156
Lymph Nodes				
Reticulo-endotheliomas (P)	5/167	4/143	5/140	6/146
Reticulo-endotheliomas (B)	0/167	1/143	0/140	0/146
Kidney				
Renal Adenoma (P)	1/179	2/164	0/145	0/160
Reticulo-endotheliomas (B)	1/179	0/164	0/145	0/160
Thyroid				
Adenoma (P)	1/145	1/117	0/127	0/137
Adenoma (B)	0/145	4/117*	1/127	0/137
"C" Cell Adenoma (P)	0/145	1/117	0/127	0/137
"C" Cell Adenoma (B)	0/145	0/117	0/127	4/137
Parathyroid				
Adenoma (B)	3/111	3/88	2/82	2/100
Adrenal				
Cortical Adenoma (B)	40/177	18/155	19/141	23/153
Cortical Adenoma (P)	6/177	5/155	3/141	4/153
Stomach				
Papilloma (B)	0/169	1/149	0/140	0/145
Basal Cell (P)	0/169	0/149	2/140	1/145
Pleura, Peritoneum Mesenteries				
Fibroma (P)	0/161	2/152	0/139	0/147
Pancreas				
Islet Cell Adenoma (B)	0/114	0/98	0/99	0/107
Small Intestine				
Adenocarcinoma (P)	1/148	1/140	0/132	0/141

TABLE 2. (CONTINUED)

TUMOR TYPE	Unexposed Controls	0.25 ppm Exposed	1.0 ppm Exposed	5.0 ppm Exposed
Colon				
Adenocarcinoma (P)	0/158	0/146	2/129	3/139
Leiomyoma (B)	0/158	0/146	0/129	1/139
Papilloma (B)	0/158	0/146	0/129	1/139
Total Tumors	0/158	0/146	2/129	5/139**
Skin				
Leiomyoma (B)	0/170	1/161	0/146	0/147
Squamous Cell Carcinoma (P)	0/170	1/161	0/146	0/147
Trichoepithelioma (B)	0/170	1/161	0/146	0/147
Hemangioma (B)	0/170	0/161	1/146	0/147
Fibroma (B)	0/170	0/161	0/146	1/147
Pituitary				
Adenoma (B)	0/163	1/133	0/129	1/138

† - Metastatic tumors in various organs were not counted.
(P) - Primary malignant tumors.
(B) - Benign tumors.
* - Significant at the 0.05 level as determined using the Fisher Exact Test.
** - Significant at the 0.01 level as determined using the Fisher Exact Test.

The nonneoplastic histopathology finding for exposed hamsters included descriptions and discussion of many lesions which occasionally occurred more frequently than in control animals. These probably reflected the aging process or the existence of chronic disease states to which hamsters are susceptible. Analysis of the incidence of such lesions would not elucidate the effect of hydrazine exposure on target organs. Therefore, the data were examined to select specific organ lesions which might have been related to exposure. This examination revealed that lesions in the nares, trachea, and bronchi (considered as one organ in the accounting), lung, liver, spleen, lymph nodes, kidney, thyroid, adrenal, colon, and testes occurred more frequently in exposed animals and could be possible sites of toxic action by hydrazine.

Two important observations emerged:

1. Degenerative disease, characterized by amyloidosis in the livers, spleens, kidneys, thyroids, adrenals; and liver hemosiderosis, kidney mineralization, general degeneration of the adrenals; and senile atrophy, aspermatogenesis, and hypospermatogenesis, is a common finding in all groups of hamsters.

2. The important fact is that these lesions occur with statistically significantly higher frequency in the exposed group; and in most cases, a dose-response relationship can be seen. The implication is that the stress of 12 months of hydrazine exposure at the various dose levels tended to increase the degenerative process in a dose-dependent manner.

Nasal epithelial tumors were observed only in hydrazine-exposed rats. The majority of the epithelial neoplasms were benign and were mainly classified as adenomatous nasal polyps. Small numbers of villous nasal polyps, muco-epidermoid papillomas, and squamous cell papillomas were also noted. The incidence of these benign and several malignant epithelial tumors (shown in Tables 3 and 4) was elevated significantly in the 5 ppm hydrazine-exposed rats of both sexes. An apparent dose-response was noted in that the incidence and degree of significance of the benign tumors were less in the 1 ppm hydrazine exposure groups (only one malignancy was found in both sexes). No tumors of this type were seen in either control group of rats, and only one malignancy of the six tumors was seen in about 400 rats exposed to 0.05 and 0.25 ppm. Most of these tumors were seen after two years with the earliest occurring in a male rat at 88 weeks (36 weeks postexposure) and in a female rat at 98 weeks.

Varying degrees of acute inflammation were observed in the nasal cavity, larynx and/or trachea in some rats from the control and all treated groups. The incidence and severity of the inflammatory changes were greatest in male and female rats from the group receiving 5.0 ppm, and in some of these affected animals, they were associated with focal hyperplasia and/or squamous metaplasia of the epithelium of the nasal cavity, larynx, and trachea. These histopathologic changes were observed in rats dying during the study as well as in the animals killed at the 2-year interim sacrifice and at the 2-1/2-year terminal sacrifice.

TABLE 3. SELECTED TUMORS FOUND IN FEMALE FISCHER 344 RATS AFTER INHALATION EXPOSURE TO HYDRAZINE

TUMOR TYPE	Unexposed Controls (N = 147)	Exposed 0.05 ppm (N = 99)	Exposed 0.25 ppm (N = 100)	Exposed 1.0 ppm (N = 97)	Exposed 5.0 ppm (N = 98)
Nasal cavity:					
Epithelial (Benign)	0 (0)	1 (1)	0 (0)	4 (4)*	31 (32)**
Epithelial (Malignant)	0 (0)	0 (0)	0 (0)	0 (0)	5 (5)**
Pituitary:					
Adenoma	59 (40)	28 (28)	35 (35)	33 (34)	40 (41)
Adenocarcinoma	9 (6)	6 (6)	2 (2)	6 (6)	6 (6)
Thyroid:					
Adenoma	9 (6)	2 (2)	4 (4)	7 (7)	7 (7)
Carcinoma	17 (12)	1 (1)	8 (8)	15 (15)	5 (5)
Adrenals:					
Pheochromocytoma	10 (7)	3 (3)	6 (6)	9 (9)	12 (12)
Uterus:					
Adenoma	1 (0)	0 (0)	0 (0)	2 (2)	3 (3)
Adenocarcinoma	10 (7)	4 (4)	5 (5)	7 (7)	6 (6)
Endometrial stromal sarcoma	0 (0)	2 (2)	1 (1)	1 (1)	3 (3)
Lymphoreticular Tissue:					
Leukemias	41 (28)**	18 (18)	21 (21)	13 (13)	13 (13)
Sarcomas	4 (3)	4 (4)	4 (4)	2 (2)	6 (6)
Mammary gland:					
Adenoma	4 (3)	4 (4)	6 (6)	8 (8)	8 (8)
Fibroadenoma	28 (19)	20 (20)	11 (11)	18 (19)	19 (19)
Adenocarcinoma	2 (1)	1 (1)	2 (2)	2 (2)	3 (3)
Liver:					
Liver cell tumor	3 (2)	0 (0)	0 (0)	6 (6)	3 (3)
Lung:					
Bronchial adenoma	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)

*Significant at the 0.05 level, control vs. test.
**Significant at the 0.01 level, control vs. test.
() = % incidence.

The more severe grades of chronic respiratory disease were observed in lungs of some rats exposed to 5.0 ppm hydrazine and to a lesser degree in males exposed at 0.05 ppm. None of the males or the females exposed to 0.25 and 1.0 ppm showed epithelial hyperplasia. The morphological changes included peribronchial/peribronchiolar lymphoid hyperplasia, pneumonia, bronchopneumonia, and bronchiectatic abscesses. The affected animals usually showed the more severe grades of acute inflammation in the nasal cavity, larynx and/or trachea but with a higher prevalence.

The incidence of focal liver cell hyperplasia tended to be greater in treated as compared to control female rats only at the exposure levels of 1.0 ppm and 5.0 ppm. This effect was seen in female rats dying during the study and in those killed at the 2-year interim sacrifice, but it was not noted in female rats killed at the 2-1/2-year terminal sacrifice. There was no difference in the incidence of liver cell hyperplasia in treated as compared to control male rats. There was no evidence that treatment with hydrazine increased the incidence of hepatic neoplasia. It was considered, therefore, that the slightly greater incidence of liver cell hyperplasia in treated as compared to control female rats arose fortuitously and that it was not related to treatment. Acute endometritis was noted more frequently in female rats from the group receiving 5.0 ppm than in the controls or in rats from the groups receiving 0.05 ppm, 0.25 ppm, or 1.0 ppm. Acute salpingitis was present only in rats from the highest dosage group with the exception of one female from the 1.0 ppm dosage level and killed at termination.

TABLE 4. SELECTED TUMORS FOUND IN MALE FISCHER 344 RATS AFTER INHALATION EXPOSURE TO HYDRAZINE

TUMOR TYPE	Unexposed Controls (N = 149)	Exposed 0.05 ppm (N = 99)	Exposed 0.25 ppm (N = 99)	Exposed 1.0 ppm (N = 98)	Exposed 5.0 ppm (N = 99)
Nasal Cavity:					
Epithelial (Benign)	0 (0)	2 (2)	2 (2)	10 (10)**	66 (67)**
Epithelial (Malignant)	0 (0)	1 (1)	0 (0)	1 (1)	6 (6)**
Pituitary:					
Adenoma	62 (42)	31 (31)	29 (29)	27 (28)	26 (26)
Adenocarcinoma	4 (3)	0 (0)	5 (5)	4 (4)	5 (5)
Thyroid:					
Adenoma	15 (10)	5 (5)	7 (7)	9 (9)	2 (2)
Adenocarcinoma	7 (5)	6 (6)	5 (5)	9 (9)	13 (13)*
Adrenals:					
Pheochromocytoma	16 (11)	14 (14)	13 (13)	18 (18)	11 (11)
Testes:					
Interstitial cell tumor	104 (70)	80 (81)	73 (74)	83 (85)	74 (75)
Prostate:					
Squamous carcinoma	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Liver:					
Liver cell tumors	9 (6)	11 (11)	8 (8)	6 (6)	4 (4)
Lung:					
Bronchial adenoma	0 (0)	0 (0)	0 (0)	0 (0)	3 (3)
Lymphoreticular Tissue:					
Leukemias	36 (24)	20 (20)	28 (28)	22 (22)	10 (10)*
Sarcomas	8 (5)	9 (9)	3 (3)	6 (6)	3 (3)

*Significant at the 0.05 level, control vs. test.
**Significant at the 0.01 level, control vs. test.
() = % incidence.

Many microscopic variations from normal were seen in the aging mice, both control and hydrazine-exposed groups. The only lesion of significance, an increased incidence of pulmonary adenomas in the 1.0 ppm hydrazine-exposed mice, is shown in Table 5. This small increase in tumor incidence over unexposed control mice is similar to that previously reported in Swiss mice (MacEwen et al.[8]). An increased incidence of ovarian tubular adenomas was also noted in the group of mice exposed to 1.0 ppm hydrazine. This increase was not significant at the 0.05 confidence level, and its biological significance is uncertain since there was no suggestion of malignancy in this type of tumor in any of the exposed or control mice. The occurrence of nonneoplastic lesions in the C57Bl/6 mice used in this study was similar in all groups with no apparent treatment effects.

Three rodent species that inhaled hydrazine concentrations of 1.0 ppm or greater for a year developed oncogenic changes in the respiratory system. These changes appeared to be dose related in the rat in which the significant effects were epithelial tumors of the nasal turbinate. In the female rat, the tumor incidence was 4% and 37%, respectively, in animals exposed to 1.0 and 5.0 ppm hydrazine. In the male rats, the incidence was 11% at 1.0 ppm and 73% at 5.0 ppm. Nasal polyps were significant only in the 5.0 ppm hydrazine-exposed hamsters. These tumors were not seen in any unexposed control rats and in only 1 of 181 unexposed control hamsters.

A previous report of hydrazine exposures (MacEwen et al.[8]) indicated a dose-related increase in alveolargenic carcinomas in female ICR mice (a strain that normally has a high incidence) exposed to 1.0 and 5.0 ppm hydrazine. C57Bl/6 mice used in this study and exposed to 1.0 ppm hydrazine exhibited a significant increase in pulmonary adenomas. This concentration was the highest level tested in mice during the present study since the prior study had shown 5.0 ppm killed half of the mice during exposure.

A number of chronic nontumorous pathologic changes were seen in rats and hamsters exposed to hydrazine concentrations of 1.0 or 5.0 ppm. Significant differences between unexposed control male rats and the high level exposure groups occurred after one month of exposure and continued even after cessation of hydrazine treatment. Both male and female rats in the 5 ppm exposure group had a much higher incidence of upper respiratory inflammation and squamous metaplasia. Male hamsters exposed to 5 ppm hydrazine had significantly lower body weights than control animals during their exposure and the 12-month postexposure holding period. Amyloidosis, a disease frequently seen in aged hamsters, was much more prevalent in the exposed groups, and the incidence appeared to be dose related. Although the mortality rates were comparable between the test and

exposure groups of hamsters throughout the study period, there were greater numbers of changes in the hydrazine-exposed animals than their unexposed controls that are usually associated with aging such as amyloidosis and senile atrophy of the testes. Analysis of the oncogenic changes and other toxic effects of exposure to hydrazine indicates that the nononcogenic sequelae were more severe in producing debilitation and lethal effects. The oncogenic changes were mostly benign and observable only at the microscopic level producing little or no impairment of respiratory function and had no effect on life expectancy.

TABLE 5. NEOPLASTIC PATHOLOGY IN CONTROL AND HYDRAZINE-EXPOSED FEMALE C57B1/6 MICE

	Set No. 1			Set No. 2	
TUMOR TYPE	Unexposed Controls (N = 385)	Exposed 0.05 ppm (N = 364)	Exposed 0.25 ppm (N = 382)	Unexposed Controls (N = 378)	Exposed 1.0 ppm (N = 379)
Pituitary:					
Adenoma	152 (39)	94 (26)	101 (26)	109 (29)	64 (17)
Carcinoma	7 (2)	10 (3)	3 (1)	8 (2)	2 (1)
Thyroid:					
Adenoma	17 (4)	25 (7)	19 (5)	34 (9)	22 (6)
Carcinoma	2 (1)	1 (0)	1 (0)	2 (1)	1 (0)
Uterus:					
Adenocarcinoma	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)
Lymphoreticular Tissue:					
Leukemias	4 (1)	5 (2)	11 (3)	5 (1)	0 (0)
Sarcomas	145 (38)	154 (42)	150 (39)	154 (41)	139 (37)
Mammary Gland:					
All tumors	1 (0)	1 (0)	0 (0)	1 (0)	0 (0)
Liver:					
Liver cell tumor	4 (1)	9 (2)	6 (2)	6 (2)	11 (3)
Lung:					
Adenoma	8 (2)	3 (1)	5 (1)	4 (1)	12 (3)*
Adenocarcinoma	2 (1)	1 (0)	2 (1)	3 (1)	3 (1)
Ovary:					
Tubular adenoma	12/369 (3)	10/340 (3)	11/365 (3)	13/365 (4)	23/361 (6)

*Significant at 0.05 level, control vs. test.
() = % incidence

The respiratory system appears to be the primary site of hydrazine induced oncogenic changes regardless of route of administration. In studies conducted by Roe et al,[10] and others, lung tumors were induced in Swiss mice after oral administration of hydrazine in water. Lung tumors were induced in C57B1/6 mice by Mirvish et al.[11] after intraperitoneal injection. Rats given hydrazine sulfate by stomach tube by Severi and Biancifiori[12] exhibited some lung tumors. No statistically significant tumor induction was seen in rodents exposed to hydrazine concentrations of 0.25 or 0.05 ppm.

CONCLUSIONS

We conclude from these studies that hydrazine is a relatively weak tumorigen which exhibits a dose-response related tumor induction at inhaled concentrations of 1.0 ppm and 5.0 ppm. Repeated exposures to hydrazine concentrations above 5.0 ppm result in early death of rodents and dogs usually associated with malnutrition after chronic exposure.

The incidence of benign and malignant tumors was highest in nasal turbinates of rats. This rat tissue has demonstrated extreme sensitivity to the action of respiratory carcinogens (HMPA and formaldehyde) and may not be directly extrapolatable to exposure of humans who are not obligate nose-breathers. Nevertheless, the toxic and oncogenic effects seen in this study indicate that the current OSHA Threshold Limit Value of 1.0 ppm for hydrazine is unsatisfactory and is too near concentrations which cause death in chronically exposed animals. More realistically, the ACGIH recommended TLV of 0.1 ppm would be expected to provide adequate protection.

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